

REMARKS

Applicants wish to thank Examiner Dutt and Supervisory Examiner Stucker for the courtesies extended during the telephone interview on August 12, 2008. The rejected claims 2-8 and 21 were discussed in view of applicants' proposed claim amendments with respect to the rejections presented in the Non-Final Office Action of May 2, 2008. Supervisory Examiner Stucker agreed that the substitution of the phrase "is capable of differentiating" with the term "differentiates" potentially provides specific functional characteristics of the claimed cells and distinguishes the claimed cells from other stem cells (Interview Summary of August 21, 2008, page 4). Although the rejections directed to these claims were not fully resolved, Examiner Stucker provided helpful guidelines and suggested how the rejections under 35 U.S.C. 102(b) over Zhao, et al. (*PNAS*, 100: 2426-2431, 2003) and under 35 U.S.C. 102(a) or 35 U.S.C. 102(e) over Reid, et al. (U.S. Patent Application Publication No. 2002/0182188) might be overcome. Specifically, the Examiner suggested that evidence to demonstrate the significance of fibronectin in deriving the claimed multipotent cell be submitted and the term "MOMC" in the claims to clarify the cell type be inserted. Finally, Examiner Stucker noted that the previously filed Declaration under 37 C.F.R. §1.132 was **not dated** and to be fully compliant must be resubmitted. Applicants respectfully resubmit herewith a Declaration under 37 C.F.R. §1.132 by Dr. Masataka Kuwana (one of the inventors) that is duly signed and dated.

Applicants believe that in view of this paper, the application is in condition for allowance. Reconsideration and withdrawal of the pending rejections are respectfully requested.

Claim Status

Claims 2-16, 19, 20, and 22 are pending after entry of this paper. Claims 2-8 have been rejected. Claims 9-16, 19-20 and 22 have been withdrawn and claims 1, 17-18 and 21 have been cancelled without prejudice. Applicants reserve the right to pursue withdrawn and cancelled claims in a continuing application. Claims 2-8 have been amended.

Claims 2, 3, and 5-8 have been amended to replace the phrase “is capable of differentiating” with the term “differentiates.” Support may be found throughout the instant specification and previously presented claims.

Claim 2 has been amended to replace the term “monocyte” with the phrase “monocyte-derived multipotent cell (MOMC).”

Claims 2-8 have been further amended to add the term “(MOMC)” based on the Examiner’s suggestion (Interview Summary – page 4).

No new matter has been introduced by these amendments. Reconsideration and withdrawal of the pending rejections in view of the above claim amendments and below remarks are respectfully requested.

Response to Rejections under 35 U.S.C. §102(b)

Claims 2-8 have been rejected under 35 U.S.C. §102(b) as being anticipated by Zhao, et al. (*PNAS*, 100: 2426-2431, 2003). Specifically, the Examiner contends that Zhao allegedly discloses the isolation of pluripotent stem cells (PSC) from human peripheral blood monocytes that resemble fibroblasts and express the monocytic and hematopoietic cellular differentiation stem cell markers, such as CD14, CD34 and CD45. While Zhao does disclose

that PSCs express type I collagen, according to the Examiner, it would be inherent (Office Action – page 5). Therefore, the Examiner concludes that Zhao allegedly anticipates the claimed invention (Office Action – page 6). Applicants respectfully disagree.

According to the Examiner, MOMC and PSC cells are allegedly structurally similar and both are **capable** of differentiating into the claimed cell types under appropriate conditions (Office Action – pages 7-8; emphasis added). Specifically, the Examiner contends that the term “capable” in the claims allegedly does not set the boundaries because “capable” means “is able to” and not necessarily “will do.” (Office Action – page 4). Applicants respectfully disagree. However, in order to expedite prosecution and without disclaimer of, or prejudice to, the subject matter recited therein, applicants have amended claims 2, 3, and 5-8 to replace the phrase “is capable of differentiating” with the term “differentiates,” addressing Examiner’s concerns over the interpretation of the term “capable” (Office Action – page 4).

Furthermore, the Examiner cites MPEP 2113, which states that product-by-process claims are limited to and defined by the process; however, the patentability of the product does not depend on its method of production (Office Action – page 7). The Examiner contends that the process steps neither relate to the claimed multipotent cells nor imply any structural limitations to the product. In order to expedite prosecution and without disclaimer of, or prejudice to, the subject matter recited therein, applicants have amended claim 2 to replace the term “monocyte” with the phrase “monocyte-derived multipotent cell (MOMC).” Therefore, the presently pending claims readily recite a process step of obtaining the monocyte-derived multipotent cell (MOMC) by culturing peripheral blood mononuclear cells (PBMC) *in vitro* on fibronectin and collecting fibroblast-like cells expressing CD14 and CD34. Whereas Zhao obtains pluripotent stem cells (PSC) by repeated stimulation of peripheral blood mononuclear

cells with high concentrations of M-CSF¹ and PMA². Applicants respectfully direct the Examiner's attention to Seta, et al. (*Keio J Med* 56(2):41-47, 2007; previously submitted) at page 45. Seta discusses in detail the criticality of the methods of selection and generation for the cell's differentiation potential *i.e.*, functional characteristics (See also Table 1 of Seta). For instance, the generation of monocytic endothelial progenitor cells (EPC) in PBMC cultures requires either fibronectin or type I collagen, but the differentiation potential of these cells is quite different from MOMCs. As requested by the Examiner, the Seta reference discloses the significance of using fibronectin, type I collagen or M-CSF/PMA. Therefore, applicants respectfully assert that the two processes of producing stem cells, *i.e.*, instant application vs. Zhao, are not only different, but also clearly produce two different cell types (MOMCs vs. PSCs) based on the specific functional characteristics of each cell type. In fact, Blau, et al. (*Cell*, 105: 892-841, 2001; cited by the Examiner) states that “[e]ven among tissue-specific stem cells, there is heterogeneity ... the ability to act as a stem cell may be a cellular function shared by numerous cell types expressing diverse genes” (Blau, page 837, paragraph bridging columns 1 and 2; emphasis added). In essence, Blau states that the functional characteristics of the cell are critical in determining the cell identity.

Therefore, one skilled in the art would have had to perform a significant amount of undue experimentation in order to use Zhao's PSCs and arrive at the claimed monocyte-derived multipotent cells (MOMC) having the same functional characteristics. For instance, the claimed MOMCs differentiate into osteoblasts (bone), skeletal myoblasts (muscle), or chondrocytes (cartilage) among others; whereas PSCs of Zhao only differentiate into macrophage (white blood cells), T lymphocyte (white blood cells), epithelial cells (skin),

¹ Macrophage-colony stimulating factor

² Phorbol myristate acetate

endothelial cells (blood vessels), neurons (nerve), and hepatocytes (liver). Moreover, the conditions under which differentiation occurs for some of these cells (See ABSTRACT of Zhao), are not applicable to the claimed MOMCs:

We have induced these cells to differentiate into mature macrophages by lipopolysaccharide, T lymphocytes by IL-2, epithelial cells by epidermal growth factor, endothelial cells by vascular endothelial cell growth factor, neuronal cells by nerve growth factor, and liver cells by hepatocyte growth factor.

The instant inventors attempted to induce differentiation of MOMC into (1) T-cells using IL-2 factor, (2) neuronal cells using nerve growth factor, (3) epithelial cells using epidermal growth factor, and (4) hepatocytes using hepatocyte growth factor as Zhao employed with PSCs. However, the results indicate that MOMCs do not differentiate into T-cells, neuronal cells, epithelial cells or hepatocytes using the methods described in Zhao. Therefore, one skilled in the art could and would deduce that MOMCs are distinct from PSCs (See the attached declaration by Dr. Kuwana).

In light of these experimental results in the inventor's declaration, and the above arguments, applicants respectfully assert that one skilled in the art would not and could not consider the claimed MOMCs to be the same as the PSCs of Zhao. Hence, the claimed MOMCs are not anticipated by the PSCs of Zhao expressly or inherently because Zhao does not disclose each and every element of the claims as presented herewith (See MPEP 2131³). Reconsideration and withdrawal of the rejections under 35 U.S.C. §102(b) of claims 2-8 as being anticipated by Zhao, et al. are respectfully requested.

³ "A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." Verdegaal Bros. v. Union Oil Co. of California, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987)."

Response to Rejections under 35 U.S.C. §§ 102(a) and 102(e)

Claims 2-8 have been rejected under 35 U.S.C. §§102(a) and 102(e) as being anticipated by Reid, et al. (U.S. Patent Application Publication No. 2002/0182188). Specifically, the Examiner contends that Reid allegedly discloses the isolation of pluripotent cells from human liver that express the monocytic and hematopoietic cellular differentiation stem cell markers, such as CD14, CD34 and CD45, and collagen type I (Office Action – page 10). The Examiner concludes that Reid allegedly anticipates the claimed invention (Office Action – page 10).

Applicants respectfully disagree.

Applicants respectfully assert that the two processes of producing stem cells as presented herein in addition to being completely different, *i.e.*, culturing peripheral blood mononuclear cells vs. fetal or adult liver cells, also produce two different cell types. For instance, the claimed monocyte-derived multipotent cell (MOMC) express CD14, CD34, CD45 and type I collagen, whereas Reid, on the other hand, obtains human liver progenitors from fetal or adult livers (para. [0100]) by selecting cells expressing CD14, CD34, CD38, and ICAM. In fact, Reid explicitly avoids selecting cells that express CD45 and glycophorin A (See paras. [0132] and [0264]). While Reid mentions various markers in claims 18, 22, and 23, applicants respectfully point out that the cells are selected explicitly that do not express CD45, *i.e.*, negative selection for CD45 (See para. [0264] or Reid). Since the Reid reference does not disclose monocyte-derived multipotent cells (MOMC) that express CD14, CD34, CD45 and type I collagen obtained by culturing peripheral blood mononuclear cells, Reid does not anticipate the claimed invention. Reconsideration and withdrawal of the rejections under 35 U.S.C. §§ 102(a) and 102(e) of claims 2-8 as being anticipated by Reid, et al. are respectfully requested.

Dependent Claims

The applicants have not independently addressed all of the rejections of the dependent claims. The applicants submit that for at least similar reasons as to why independent claim 2 from which all of the dependent claims 3-8 depend are believed allowable as discussed *supra*, the dependent claims are also allowable. The applicants however, reserve the right to address any individual rejections of the dependent claims and present independent bases for allowance for the dependent claims should such be necessary or appropriate.

Thus, applicants respectfully submit that the invention as recited in the claims as presented herein is allowable over the art of record, and respectfully request that the respective rejections be withdrawn.

CONCLUSION

Based on the foregoing amendments and remarks, the applicants respectfully request reconsideration and withdrawal of the pending rejections and allowance of this application. The applicants respectfully submit that the instant application is in condition for allowance. Entry of the amendment and an action passing this case to issue is therefore respectfully requested. In the event that a telephone conference would facilitate examination of this application in any way, the Examiner is invited to contact the undersigned at the number provided. Favorable action by the Examiner is earnestly solicited.

AUTHORIZATION

The Commissioner is hereby authorized to charge any additional fees which may be required for consideration of this Amendment to Deposit Account No. **13-4500**, Order No. 4439-4036.

In the event that an extension of time is required, or which may be required in addition to that requested in a petition for an extension of time, the Commissioner is requested to grant a petition for that extension of time which is required to make this response timely and is hereby authorized to charge any fee for such an extension of time or credit any overpayment for an extension of time to Deposit Account No. **13-4500**, Order No. 4439-4036.

Respectfully submitted,
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